Synthesis and Application of Tetrahydro-2H-fluorenes by a Pd(0)-Catalyzed Benzylic C(sp^3)-H Functionalization

AUTHOR(S):

Suetsugu, Satoshi; Muto, Nobusuke; Horinouchi, Misa; Tsukano, Chihiro; Takemoto, Yoshiji

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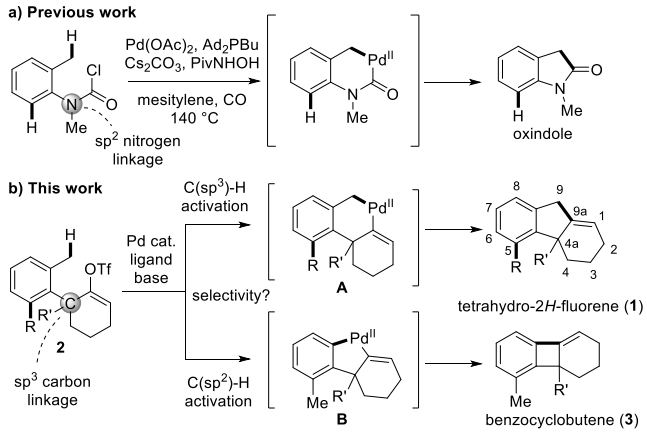
COMMUNICATION

Synthesis and application of tetrahydro-2*H*-fluorenes via a Pd(0)-catalyzed benzylic C(sp^3)–H functionalization

Satoshi Suetsugu, Nobusuke Muto, Misa Horinouchi, Chihiro Tsukano and Yoshiji Takemoto*[a]

Abstract: A new method has been developed for the synthesis of tetrahydro-2*H*-fluorene based on a Pd(0)-catalyzed benzylic C(sp^3)–H functionalization. Importantly, the success of the cyclization step was dependent on there being substituents at the two positions ortho to the benzylic group to avoid an undesired C(sp^2)–H functionalization. This method was subsequently used to prepare the right-hand fragment of the hexacyclic triterpenoid benzohopane. This method therefore represents a powerful tool for the construction of the related compounds.

Pd(0)-catalyzed C–H functionalization has attracted considerable attention for the development of increasingly straightforward synthetic routes with better atom and step economies than conventional methods using relatively unactivated C–H bonds.[1,2] This transformation is effective for intramolecular cyclization, and several methods have been developed to date for the construction of carbocycles[3] and heterocycles.[4,5] For example, Baudoin and co-workers recently reported the synthesis of a series of strained γ-lactams by Pd(0)-catalyzed C(sp^3)–H alkenylation.[5c] Furthermore, we recently reported the synthesis of oxindoles, 2-arylindoles, pyrrolophenanthridines and indoloquinazolinones using Pd(0)-catalyzed C(sp^3)–H functionalization (Scheme 1a).[6]



Scheme 1. Pd(0)-catalyzed benzylic C(sp^3)–H activation for the synthesis of oxindoles and tetrahydro-2*H*-fluorenes.

[a] S. Suetsugu, N. Muto, M. Horinouchi, Dr C. Tsukano, Prof. Dr Yoshiji Takemoto
Graduate School of Pharmaceutical Sciences
Kyoto University
Yoshida, Sakyo-ku, Kyoto 606-8501, Japan
E-mail: takemoto@pharm.kyoto-u.ac.jp
Supporting information for this article is given via a link at the end of the document.

Tetrahydrofluorenes, which consist of an all-carbon tricyclic core, have been used as intermediates for the synthesis of several terpenoids, including benzohopanes,[7a,b] aethiosides[7c] and pelorol[7d] via the derivatization of a suitably positioned double bond (Figure 1). In particular, tetrahydro-2*H*-fluorene (**1**), bearing a double bond between its C1 and C9a positions, would be a useful building block for the introduction of other functional groups and the construction of increasingly complex structures, such as benzohopane. However, compared with other tetrahydro-*1H*-fluorenes, there have been very few synthetic methods reported for the construction of **1**, including a Friedel–Crafts reaction followed by a dehydration step,[8a,b] and a Diels-Alder reaction.[7c] These reactions have been limited by their requirement for high-pressure conditions and strong acids, which make it difficult to control the regioselectivity because of double-bond isomerization. Although several other methods have been reported for the synthesis of tetrahydro-*1H*-fluorenes, including C(sp^2)–H activation,[9] these methods cannot be applied to synthesis of tetrahydro-2*H*-fluorene. The development of an improved method for the practical synthesis of tetrahydro-2*H*-fluorene is therefore strongly desired. Based on our previous reports,[6] it was envisioned that the core structure of **1** could be constructed using Pd(0)-catalyzed C(sp^3)–H functionalization chemistry from enol triflate **2** bearing an ortho-tolyl group (Scheme 1b).

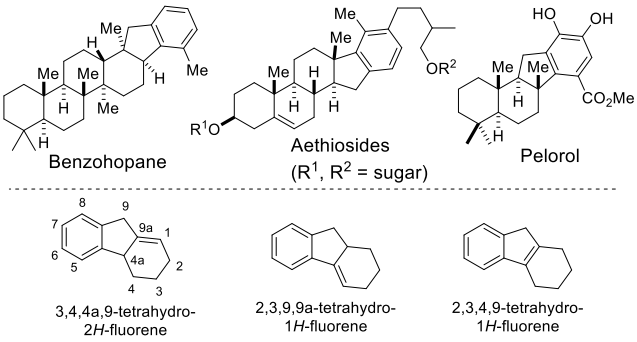


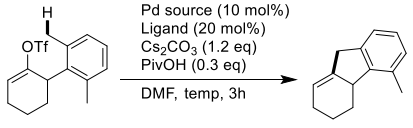
Figure 1. Natural products containing hexahydrofluorene and tetrahydrofluorene cores.

Although enol triflates are useful synthetic intermediates, there have been very few examples of their use in Pd(0)-catalyzed C(sp^3)–H activation[10] compared with C(sp^2)–H activation.[11] Compared with the synthesis of oxindoles, where we only observed C(sp^3)–H activation, C(sp^2)–H activation would compete with C(sp^3)–H activation during the synthesis of **1** because an sp^3 carbon linkage is more flexible than an sp^2 nitrogen linkage. The oxidative addition of **2** to Pd(0) would be followed by the formation of six- and five-membered palladacycles (**A** and **B**), depending on the nature of the

activation, which would undergo reductive elimination reactions to give tetrahydro-2*H*-fluorene (**1**) and benzocyclobutene (**3**), respectively. The results of this study revealed that the nature of the substituents ortho to the benzylic group of enol triflate **2** were critical for controlling the chemo-selectivity of this cyclization reaction. Furthermore, the use of tetrahydro-2*H*-fluorene **2** was considered to be advantageous for further transformations based on its double bond. Thus, we also planned to synthesize the right-hand segment of benzohopane. Herein, we report the development of a Pd(0)-catalyzed benzylic C(sp^3)–H activation for the synthesis of tetrahydro-2*H*-fluorene and its subsequent application to synthetic studies concerning benzohopane.

We initially used enol triflate **2a** bearing a methyl group at each one of its ortho positions as a model substrate because of its potential application to the synthesis of benzohopane. The treatment of **2a** with $Pd(PPh_3)_4$ (10 mol%), Cs_2CO_3 (1.1 equiv.) and pivalic acid (30 mol%) in DMF at 140 °C gave tetrahydro-2*H*-fluorene **1a** (Table 2, entry 1). We subsequently screened a variety of different palladium sources and ligands. Although several palladium catalysts, including $Pd(OAc)_2$ and $Pd_2(dba)_3$, gave comparable yields to $Pd(PPh_3)_4$, the use of $Pd(OCOCF_3)_2$ with PPh_3 afforded the best results of all of the catalysts (Table 2, entries 2–4). The use of bulky trialkyl phosphine ligands, including Cy_3P, Ad_2PBu and tBu_3P, which were effective for our oxindole synthesis[6a,c] through C(sp^3)–H activation, resulted in low yields (Table 2, entries 5–7). The reaction temperature and additives were also optimized. Interestingly, the reaction proceeded well at 80 or 100 °C, which were both lower than the temperature required of our oxindole synthesis. This result can be explained in terms of the greater accessibility of the palladium center to the benzylic C(sp^3)–H bond because of the flexible sp^3 carbon linkage. Carboxylic acids were found to be essential as additives, with 1-AdCOOH giving better results (Table 2, entries 8–11). These results indicated that this reaction proceeded through a concerted metalation deprotonation (CMD) pathway, as previously reported.[4c,12] The optimized conditions were therefore determined to be as follows: $Pd(OCOCF_3)_2$ (10 mol%), PPh_3 (20 mol%), Cs_2CO_3 (1.2 equiv.) and pivalic acid (30 mol%) in DMF at 80–100 °C.

Table 1. Investigation of the reaction conditions for the synthesis of tetrahydro-2*H*-fluorenes through Pd(0)-catalyzed C(sp^3)–H activation.

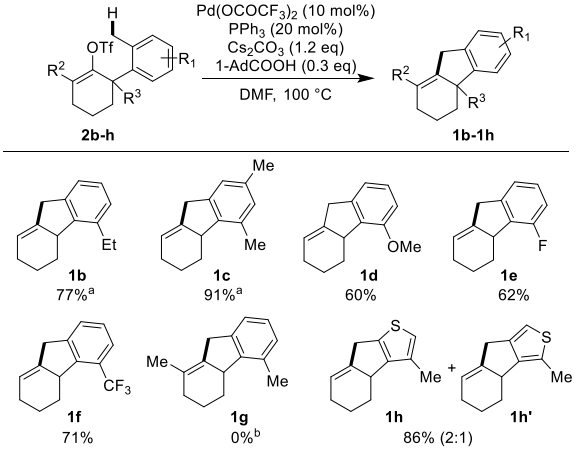


2a **1a**

entry	Pd source	ligand	additive	Temp	Yield[a]
1	$Pd(PPh_3)_4$	none	PivOH	140 °C	69%
2	$Pd(OAc)_2$	PPh_3	PivOH	140 °C	64%
3	Pd_2dba_3	PPh_3	PivOH	140 °C	60%
4	$Pd(OCOCF_3)_2$	PPh_3	PivOH	140 °C	83%
5	$Pd(OCOCF_3)_2$	Cy_3P	PivOH	140 °C	35%
6	$Pd(OCOCF_3)_2$	Ad_2PnBu	PivOH	140 °C	29%
7	$Pd(OCOCF_3)_2$	$PtBu_3$	PivOH	140 °C	29%
8	$Pd(OCOCF_3)_2$	PPh_3	PivOH	100 °C	93%
9	$Pd(OCOCF_3)_2$	PPh_3	None	100 °C	0%
10	$Pd(OCOCF_3)_2$	PPh_3	1-AdCOOH	100 °C	98%
11	$Pd(OCOCF_3)_2$	PPh_3	1-AdCOOH	80 °C	99%

[a] Isolated yield.

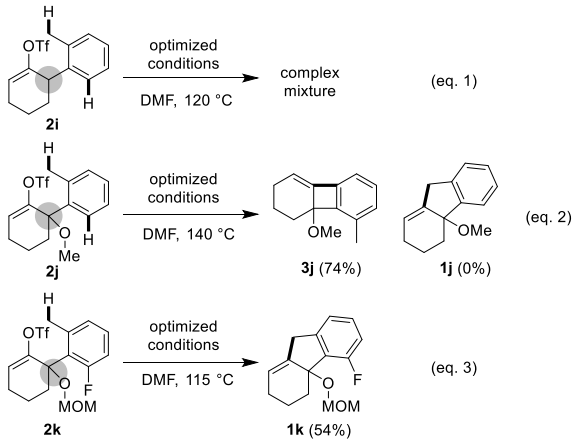
With the optimized conditions in hand, we proceeded to investigate the scope of this reaction for the synthesis of various tetrahydro-2*H*-fluorenes (Scheme 2). Enol triflate substrates **2b–f** bearing electron-withdrawing or electron-donating group such as alkyl, methoxy, fluorine and trifluoromethyl groups all reacted smoothly to afford the corresponding tetrahydro-2*H*-fluorenes **1b–f** in 60–91% yields. In the case of **2b**, the C(sp^3)–H activation reaction only occurred at the benzylic methyl group in the presence of a benzylic methylene group. Notably, all of these products were unstable and readily decomposed following a few days at room temperature. When the tetra-substituted enol triflate **2g** was treated under these conditions, the starting material was recovered unchanged, presumably because of the difficulties associated with the oxidative addition of a congested enol triflate to Pd(0). The reaction of substrate **2h** bearing a thiophenyl group instead of a phenyl group proceeded smoothly, albeit with low regioselectivity (**1h**:**1h'** = 2:1). It is noteworthy that the isomerization of the olefin in products **1b–h** was not observed under the optimized conditions.



Scheme 2. Scope and limitations of the Pd(0)-catalyzed benzylic C(sp^3)–H alkenylation. [a] 80 °C, [b] The starting material was recovered.

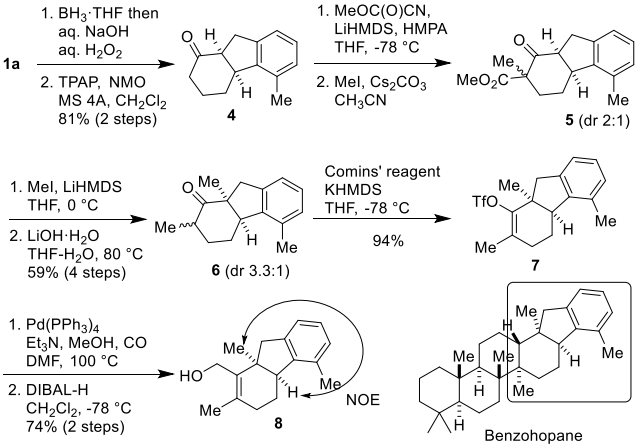
We also examined the substituent effects of the ortho and linkage positions. Substrate **2i**, bearing only one ortho-methyl group on its phenyl ring, was identified as a good substrate to determine whether C(sp^3)–H activation was preferred to C(sp^2)–H activation under the optimized conditions. When substrate **2i** was reacted at 120 °C,[13] we observed a complex mixture of products. However, the reaction of the analogous substrate **2j** bearing a methoxy group at its linkage position, proceeded exclusively by C(sp^2)–H activation to give benzocyclobutene **3j**

in 74% yield without any tetrahydro-2*H*-fluorene **1j** (Scheme 3, eqs. 1 and 2). These results therefore indicated that a substituent was required at both of the ortho positions on the phenyl ring to allow for the successful formation of tetrahydro-2*H*-fluorenes **1**. Substrate **2k** bearing a fluorine atom instead of a hydrogen atom at the other ortho position was also evaluated to disclose whether the second ortho position requires a sterically bulky group such as methyl group or not. The reaction of **2k** gave tetrahydro-2*H*-fluorene **1k** in a 54% yield (eq.3). This result indicated that the bulky group was not essential in the second ortho position, and blocking the position by non-hydrogen atom was more important. Furthermore, a comparison of the reactions of **2e** and **2k** revealed that the introduction of a methoxymethyl (MOM) ether substituent at the linkage position did not affect the benzylic C(sp^3)–H activation. However, the nature of the substituents at the linkage positions appeared to be sterically important for C(sp^2)–H activation.



Scheme 3. Investigation of the substituent effect. Reaction conditions: $Pd(OCOCF_3)_2$ (10 mol%), PPh_3 (20 mol%), Cs_2CO_3 (1.2 equiv.) and 1-AdCOOH (0.3 equiv.) in DMF.

To highlight the utility of our newly developed reaction for the preparation of tetrahydro-2*H*-fluorenes, we investigated its application to the synthesis of the right-hand segment of benzohopane. Benzohopanes have been isolated from rock extractions and petroleum samples collected from Guatemala.[7a,b] While these natural products have not been detected in living organisms, they are generated by the aromatization of C35 hopanoids via an interesting mechanism. Notably, there have been no synthetic studies reported to date concerning these compounds. Our synthesis of the right-hand segment of benzohopane started from freshly prepared **1a**, which was subjected to sequential hydroboration and oxidation reactions[14] to give the cis-fused structure in **4** (Scheme 4). The subsequent installation of an ester group, followed by stepwise methylation reactions and the hydrolysis/decarboxylation of the ester group gave methyl ketone **6** as a 3.3:1 mixture along with a small amount of the corresponding trans-fused isomers.[15] Triflation using Comins' reagent[15] gave triflate **7**, which was treated with Et_3N, MeOH and a catalytic amount of $Pd(PPh_3)_4$ in DMF under CO at 100 °C to give an α,β-unsaturated ester containing a tetra-substituted olefin. Finally, the right-hand fragment of benzohopane **8** was synthesized by DIBAL-H reduction. The cis-fused stereochemistry of **8** was confirmed by NOE experiments.



Scheme 4. Synthesis of a right-hand fragment **8** of benzohopane.

In summary, we have developed a new method for the synthesis of tetrahydro-2*H*-fluorenes via Pd(0)-catalyzed benzylic C(sp^3)–H activation. Importantly, the success of this reaction is dependent on there being a substituent at both of the ortho positions to favor the necessary C(sp^3)–H functionalization. This newly developed method for the synthesis of tetrahydro-2*H*-fluorenes was subsequently applied to the synthesis of the right-hand fragment of benzohopane, highlighting its utility. This method therefore represents a powerful tool for the construction of related compounds.

Acknowledgments

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Keywords: C-H functionalization • Palladium • Tetrahydrofluorene • Benzohopane • Cyclization

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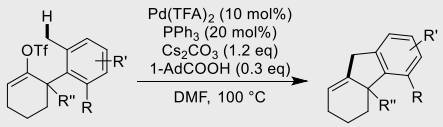

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A new method has been developed for the synthesis of tetrahydro-2*H*-fluorenes based on the Pd(0)-catalyzed benzylic C(sp^3)–H alkenylation of an enol triflate bearing substituents at its two ortho positions. This method was used to prepare the right-hand fragment of benzohopanes.